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10/052,417	01/17/2002	David Harrow Gelfand	1803-0329-999	4095

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,417	GELFAND ET AL.	
	Examiner	Art Unit	
	Jehanne S Sitton	1634	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-52 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-54 are pending in the instant application. The following office action contains new grounds of rejection. Upon further review and search, the instantly pending claims have been reassessed in light of teachings in the art and Dr. Gelfand's declaration submitted 1/3/2003. The following rejections constitute the complete set being presently applied to the instantly pending claims. This action is NON-FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 1-54 under Obviousness type Double Patenting, made at section 3 of the previous office action, is withdrawn in view of the filing of a terminal disclaimer, in the response of 9/3/2004.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Indefinite

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-52 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims include the term "native form" of a sequence, however it is unclear what structure such refers to. While the specification defines 'native' as "from a naturally occurring source", no specific structure is given, such that it is unclear which 'naturally occurring source" is being referred to. It is unclear if such refers to the wild type sequence of a specific polymerase which occurs in nature or to any of SEQ ID NOS 1-4 or other SEQ ID NO: recited in the claims. The issue is even more confusing given the dependency of certain claims. For example, claim 1 stipulates that the native sequence is SEQ ID NO: 1 which has a Pro at position 8, however claim 4 limits claim 1 to sequences from Thermosphipho africanus, Bacillus caldotenax, and Bacillus stearothermophilus, whereas the specification teaches such normally have a Ser, Ser, or Thr at such position.

Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for thermostable DNA polymerases comprising SEQ ID NO: 1 from Thermus species wherein position 4 of SEQ ID NO: 1 is mutated in comparison to the native sequence except that position 4 is not Glu, and wherein the thermostable polymerase has a level of discrimination against the incorporation of nucleotides labeled with flourescein family dyes which is reduced in comparison to a polymerase with Glu at position 4, nucleic acids encoding such polymerases, as well as kits comprising such, and methods of amplification and sequencing using such polymerases, does not reasonably provide enablement for the instantly recited claims

specified above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to DNA polymerases which comprise SEQ ID NO: 1 and wherein position 4 of the SEQ ID NO: 1 is mutated in comparison to the native sequence except that position 4 is not Glu, and wherein the thermostable polymerase has a level of discrimination against the incorporation of nucleotides labeled with flourescein family dyes which is reduced in comparison to the native form of the polymerase. The claims further limit the identity of amino acid position of SEQ ID NO: 1 to include specific amino acids, and further limit the polymerase to be from a specific genus or species. The claims are further drawn to nucleic acids encoding such polymerases, as well as kits comprising such, and methods of amplification and sequencing using such polymerases. The claims do not make clear which 'native' sequence the comparison is being made to. While the specification defines 'native' as "from a naturally occurring source",

no specific structure is given, such that it is unclear which 'naturally occurring source" is being referred to. It is unclear if such refers to the wild type sequence of a specific polymerase which occurs in nature or to any of SEQ ID NOS 1-4. The issue is even more confusing given the dependency of certain claims. For example, claim 1 stipulates that the native sequence is SEQ ID NO: 1 which has a Pro at position 8, however claim 4 limits claim 1 to sequences from Thermosphipho africanus, Bacillus caldotenax, and Bacillus stearothermophilus, whereas the specification teaches such normally have a Ser, Ser, or Thr at such position. Even if the term "native" is interpreted to only encompass the wild type sequence of a specific polymerase which was naturally occurring at the time the invention was made, the scope of the claims does not bear a reasonable correlation to the scope of enablement provided by the specification, or to the results shown in Dr. Gelfand's declaration of 1/3/2003. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art".

The specification teaches that the use of fluorescent dyes is important for many in vitro DNA applications. The specification teaches producing template dependent thermostable DNA polymerase enzymes having reduced discrimination against incorporation of nucleotides labeled with fluorescein family dyes (see p. 2, lines 22-25). The specification teaches that a recombinant Taq DNA polymerase enzyme which contained two mutations was constructed. The first was an E to K mutation at position 4 of the critical motif of the invention (see p. 4, lines 24-26). The

specification teaches that this mutation identified a region in the DNA polymerase gene that affects the ability of the polymerase to interact with negatively charged fluorescent nucleotides. The specification teaches that this site, distal to helix O is at the end of the Oa helix and the beginning of the Ob helix of the polymerase (see p. 12, lines 24-28). The specification teaches that based on molecular modeling principles, changes in the structure of the Oa-Ob helix other than E (Glu) to K (Lys) are also expected to produce changes in the ability of the polymerase to discriminate against nucleotides labeled with fluorescein family dyes. In response to rejections under 112/1st paragraph made in parent application 09/146,631, a declaration under 35 USC 1.132 was submitted by Dr. Gelfand for the instantly pending application. The declaration showed that for Tth polymerase, when position 4 of SEQ ID NO: 1 was mutated to any of the 19 amino acids other than Glu, the polymerase showed reduced discrimination against the incorporation of nucleotides labeled with HEX-2-PA, a flourescein family dye analog. However, it should be noted that the 19 mutants did not show the same level of reduced discrimination. As shown in the specification at page 15, polymerases from Thermatoga species and Thermosipho africanus have an Arginine (Arg, R) at position 4 while Bacillus species have an Asparagine (Asp, N) at position 4. However, the declaration shows that Arginine showed the most reduced level of discrimination while Asparagine was not the least reduced, for example Aspartate (D) showed a level of discrimination that was less reduced (see Figure 1 of declaration of 1/3/2003). Additionally, Figure 1 of the declaration shows that no pattern of predictability exists with regard to polarity, charge, or size of amino acid side chains for specific levels of reduction in discrimination in comparison to an E at position 4. While all 19 mutants showed reduced discrimination, some were more reduced than others, and it is unclear what the specific cause of

such effect is, other than the fact that E is not present. For example, while R is the most reduced, another positively charged side chain, histidine (his, H) is less reduced than a non charged, non polar side chain, glycine (Gly, G) (1.45 vs .66). Accordingly, it is clear that if in fact, position 4 of SEQ ID NO: 1 is the "critical" position with regard to the discrimination of incorporation of nucleotides labeled with fluorescein family dyes as asserted in the specification and declaration, the claims are of such a broad scope as to include polymerases, where if position 4 was mutated in comparison to wild type, such polymerases would in fact not be predictably expected to have reduced discrimination against the incorporation of fluorescein family dyes. It is also further noted that certain claims are specifically drawn to embodiments (polymerases from Thermus africanus as well as polymerases from Thermatoga) where no mutation at position 4 would be predictably expected to produce a mutant polymerase with the function recited in the claims given the results shown in the declaration.

While the claims encompass polymerases comprising SEQ ID NO: 1, 2, 3, or 4, and such SEQ ID NOS: contain additional undefined amino acid positions, the specification has not provided any teaching or guidance as to any mutation at such positions which would lead to a mutant polymerase with reduced discrimination against the incorporation of nucleotides labeled with flourescein family dyes. While molecular modeling techniques exist, such techniques would not be expected to predict which other mutation in any of SEQ ID NO: 1-4 would result in a mutant polymerase with reduced discrimination against the incorporation of nucleotides labeled with flourescein family dyes. The state of the art with regard to molecular modeling is unpredictable, as evidenced by the teachings of Lomize (Lomize et al, Proteins: Structure, Function and Genetics, suppl. 3, pp 199-203, 1999 : "Prediction of Protein Structure: The

Problem of Fold Multiplicity"). Such modeling requires the incorporation of many different parameters, including but not limited to burial of non polar side chains, saturation of hydrogen bonding potential, and stereochemical quality. Lomize teaches that many different structures are possible that can simultaneously satisfy these criteria and therefore additional energy contributions must be taken into affect (p. 199, col 2). Lomize teaches attempting to model four CASP3 target, using simple modeling procedure (see abstract). Lomize teaches that although this approach allows construction of 3D models that in some cases properly reproduce the structural class of the protein the four models predicted were incorrect (see abstract, and p. 200, col 2). Lomize teaches that such results indicate that hydrophobicity patters do not unequivocally determine protein folds. Thus from the teaching of Lomize, the skilled artisan would have recognized that molecular modeling is not yet a precise science, and that relying on such to predict the function of a particular residue is unpredictable, especially given that the specification does not teach how the residue functions to achieve the desired result or the specific programs, algorithms and parameters that the skilled artisan would use (as Lomize teaches that such are important in predicting structure or function) to determine which residues would give the desired results. Further, as shown by declaration of 1/3/2003 at figure 1, the effect of each specific amino acid change is unpredictable with regard to level of reduction in discrimination (even for position 4 which the specification and declaration assert as the "critical position" no pattern of predictability exists with regard to polarity, charge, or size of amino acid side chains for specific levels of reduction in discrimination for the other 19 possible mutants). Therefore, based on the lack of guidance in the specification, the conflicting evidence of the declaration submitted 1/3/2003, and the unpredictability taught in the art, it would require undue

experimentation for the skilled artisan to practice the invention commensurate in scope with the claims. In the instant application, the claims encompass, as well as specifically recite in certain cases, embodiments which would not be predictably expected to yield mutant polymerases with the claimed function. Neither the specification nor the art provide any guidance as to which polymerases or what structures would fall within the scope of the claims (ie, mutation at positions in the recited SEQ ID NOS other than position 4), especially with regard to polymerases from Thermosipho africanus, and Thermatoga.

Written Description

8. Claims 1-52 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to DNA polymerases which comprise SEQ ID NO: 1 and wherein position 4 of the SEQ ID NO: 1 is mutated in comparison to the native sequence except that position 4 is not Glu, and wherein the thermostable polymerase has a level of discrimination against the incorporation of nucleotides labeled with flourescein family dyes which is reduced in comparison to the native form of the polymerase. The claims further limit the identity of amino acid position of SEQ ID NO: 1 to include specific amino acids, and further limit the polymerase to be from a specific genus or species. The claims are further drawn to nucleic acids encoding such polymerases, as well as kits comprising such, and methods of amplification and sequencing using such polymerases. The claims do not make clear which 'native' sequence the comparison

is being made to. While the specification defines 'native' as "from a naturally occurring source", no specific structure is given, such that it is unclear which 'naturally occurring source" is being referred to. It is unclear if such refers to the wild type sequence of a specific polymerase which occurs in nature or to any of SEQ ID NOS 1-4. The issue is even more confusing given the dependency of certain claims. For example, claim 1 stipulates that the native sequence is SEQ ID NO: 1 which has a Pro at position 8, however claim 4 limits claim 1 to sequences from Thermosphipho africanus, Bacillus caldotenax, and Bacillus stearothermophilus, whereas the specification teaches such normally have a Ser, Ser, or Thr at such position. Even if the term "native" is interpreted to only encompass the wild type sequence of a specific polymerase which was naturally occurring at the time the invention was made, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification teaches that the use of fluorescent dyes is important for many in vitro DNA applications. The specification teaches producing template dependent thermostable DNA polymerase enzymes having reduced discrimination against incorporation of nucleotides labeled with fluorescein family dyes (see p. 2, lines 22-25). The specification teaches that a recombinant Taq DNA polymerase enzyme which contained two mutations was constructed. The first was an E to K mutation at position 4 of the critical motif of the invention (see p. 4, lines 24-26). The specification teaches that this mutation identified a region in the DNA polymerase gene that affects the ability of the polymerase to interact with negatively charged fluorescent nucleotides. The specification teaches that this site, distal to helix O is at the end of the Oa helix and the

beginning of the Ob helix of the polymerase (see p. 12, lines 24-28). The specification teaches that based on molecular modeling principles, changes in the structure of the Oa-Ob helix other than E (Glu) to K (Lys) are also expected to produce changes in the ability of the polymerase to discriminate against nucleotides labeled with fluorescein family dyes. In response to rejections under 112/1st paragraph made in parent application 09/146,631, a declaration under 35 USC 1.132 was submitted by Dr. Gelfand for the instantly pending application. The declaration showed that for Tth polymerase, when position 4 of SEQ ID NO: 1 was mutated to any of the 19 amino acids other than Glu, the polymerase showed reduced discrimination against the incorporation of nucleotides labeled with HEX-2-PA, a flourescein family dye analog. However, it should be noted that the 19 mutants did not show the same level of reduced discrimination. As shown in the specification at page 15, polymerases from Thermatoga species and Thermosipho africanus have an Arginine (Arg, R) at position 4 while Bacillus species have an Asparagine (Asp, N) at position 4. However, the declaration shows that Arginine showed the most reduced level of discrimination while Asparagine was not the least reduced, for example Aspartate (D) showed a level of discrimination that was less reduced (see Figure 1 of declaration of 1/3/2003). Accordingly, it is clear that if in fact, position 4 of SEQ ID NO: 1 is the "critical" position with regard to the discrimination of incorporation of nucleotides labeled with fluorescein family dyes as asserted in the specification and declaration, the claims are of such a broad scope as to include polymerases, where if position 4 was mutated in comparison to wild type, such polymerases would in fact not be predictably expected to have reduced discrimination against the incorporation of fluorescein family dyes. It is also further noted that certain claims are specifically drawn to embodiments (polymerases from Thermus africanus as well as polymerases

from Thermatoga) where no mutation at position 4 would be predictably expected to produce a mutant polymerase with the function recited in the claims given the results shown in the declaration. While the claims encompass polymerases comprising SEQ ID NO: 1, 2, 3, or 4, and such SEQ ID NOS: contain additional undefined amino acid positions, the specification has not provided any teaching or guidance as to any mutation at such positions which would lead to a mutant polymerase with reduced discrimination against the incorporation of nucleotides labeled with flourescein family dyes.

The claims encompass a large genus of polymerases that have not been taught or described by the specification. The mutant polymerase taught by the specification is not representative of this large genus. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides or proteins, regardless of the complexity or simplicity of the method of isolation. "Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required." See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-3, 9-13, 19, 20, 39, 40, 43, and 44 are rejected under 35 USC 102(e) as being anticipated by Hughes (Hughes et al; US Patent 6,015,668).

Hughes teaches a mutant recombinant DNA polymerase (SEQ ID NO: 3 of Hughes) from Thermatoga (Tne) which is encoded by a nucleic acid sequence (SEQ ID NO: 2 of Hughes), wherein the polymerase comprises the sequence LeuSerValArgLeuGlyIleProValLysGlu (residues 741-751). The residue at position "4" is Arg (not mutated to Glu) and the residue at position "7" is Ile, thus meeting the limitations of claims 1-3, 9-13, 19, and 20. With regard to the limitation in claim 1, for example, which states "said 'Xaa' at position 4 is mutated in comparison to said native sequence, except that 'Xaa' at position 4 is not mutated to Glu" the term "native" has been broadly interpreted. The claims do not make clear which 'native' sequence the comparison is being made to. While the specification defines 'native' as "from a naturally occurring source", no specific structure is given. It is unclear if such refers to the wild type sequence of a specific polymerase which occurs in nature or to any of SEQ ID NOS 1-4 recited in the claims. The issue is even more confusing given the dependency of certain claims. For example, claim 1 stipulates that the native sequence is SEQ ID NO: 1 which has a Pro at position 8, however claim 4 limits claim 1 to sequences from Thermosphipho africanus, Bacillus caldotenax, and Bacillus stearothermophilus, whereas the specification teaches such normally have a Ser, Ser, or Thr at such position. Therefore, the term 'native' has been broadly interpreted to be the specific SEQ ID NO: set forth in the claim. For example, in claim 1, the 'native' sequence has an Xaa, which is any amino acid at position 4. Additionally, it is noted that limitations which state "said thermostable DNA polymerase has a level of discrimination against incorporation of nucleotides labeled with fluorescein family dyes which is reduced [at least 3 fold lower or 5 fold lower] in comparison to the native form of said polymerase" is considered an inherent property of the polymerase of Hughes as the claimed sequence and the

sequence of Hughes have the same structure. Additionally, Hughes teaches that Tne mutants provide for good incorporation of dye terminators, such dye terminators can be reduced 500 fold (see col. 18, lines 25-30). With regard to claim 39, it is noted that the term 'kit' has been given no weight as it does not distinguish the claim structurally, for example, from a composition. Further, Hughes teaches packaging the polymerases in kit format (see cols 16 and 17).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 21-23, 28-34, 37-38, 45, 48-50, and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes in view of Wiemann (Wiemann et al; Analytical Biochemistry, vol. 234, pages 166-174, 1996).

Hughes teaches a mutant recombinant DNA polymerase (SEQ ID NO: 3 of Hughes) from Thermatoga (Tne) which is encoded by a nucleic acid sequence (SEQ ID NO: 2 of Hughes), wherein the polymerase comprises the sequence LeuSerValArgLeuGlyIleProValLysGlu (residues 741-751). The residue at position "4" is Arg (not mutated to Glu) and the residue at position "7" is Ile, thus meeting the limitations of claims 1-3, 9-13, 19, and 20. With regard to the limitation in claim 1, for example, which states "said 'Xaa' at position 4 is mutated in comparison to said native sequence, except that 'Xaa' at position 4 is not mutated to Glu" the term "native" has been broadly interpreted. The claims do not make clear which 'native' sequence the comparison is being made to. While the specification defines 'native' as "from a naturally occurring source", no specific structure is given. It is unclear if such refers to the wild type sequence of a specific polymerase which occurs in nature or to any of SEQ ID NOS 1-4 recited in the claims. The issue is even more confusing given the dependency of certain claims. For example, claim 1 stipulates that the native sequence is SEQ ID NO: 1 which has a Pro at position 8, however claim 4 limits claim 1 to sequences from Thermosphipho africanus, Bacillus caldotenax, and Bacillus stearothermophilus, whereas the specification teaches such normally have a Ser, Ser, or Thr at such position. Therefore, the term 'native' has been broadly interpreted to be the specific SEQ ID NO: set forth in the claim. For example, in claim 1, the 'native' sequence has an Xaa, which is any amino acid at position 4. Additionally, it is noted that limitations which state "said thermostable DNA polymerase has a level of discrimination against incorporation of nucleotides labeled with fluorescein family dyes which is reduced [at least 3 fold lower or 5 fold lower] in comparison to the native form of said polymerase" is considered an inherent property of the polymerase of Hughes as the claimed sequence and the

sequence of Hughes have the same structure. Additionally, Hughes teaches that Tne mutants provide for good incorporation of dye terminators, such dye terminators can be reduced 500 fold (see col. 18, lines 25-30). Further, Hughes teaches packaging the polymerases in kit format (see cols 16 and 17), along with detectably labeled nucleotides, including dye terminators, which can be labeled with fluorescent dyes and which also include rNTP (see col. 8, lines 26-41). Further, Hughes teaches that the Tne polymerase can be used in methods of fluorescent sequencing, which inherently produces labeled DNA and labeled primer extension products. With regard to claims 21-23, 28-34, 37-38, 45, 48-50, and 53-54, Hughes does not specifically teach the use of or packaging of nucleotides labeled with a negatively charged fluorescent dye or a flourescein family dye, however Wiemann specifically teaches an improved method of fluorescent DNA sequencing which uses a nucleotide (specifically a dye terminator) which is labeled with fluorescein, which is a negatively charged fluorescent dye (see page 167). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the improved method of fluorescent DNA sequencing in the method of sequencing of Hughes because Wiemann teaches that this technique allows one to obtain simultaneously two independent sequences from one sequencing reaction (see page 166, abstract). It would have been further obvious to one of ordinary skill in the art to include such in the packaged nucleotides of Hughes in order to make the method of Hughes in view of Wiemann easier and more convenient to perform.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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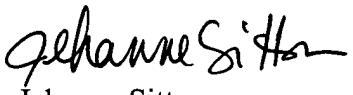

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Art Unit 1634